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Soft Tissue Sarcomas: Preoperative Versus Postoperative Radiotherapy

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External beam radiation may be given either before or after excision of a primary soft tissue sarcoma. This study was undertaken to determine whether or not the timing of radiotherapy was associated with any difference in either local control, survival, or incidence of complications. The files of 112 patients with a primary, nonmetastatic, extremity soft tissue sarcoma, treated with limb salvage surgery and irradiation were evaluated. Data regarding tumor stage, grade, site, surgical margin, dosage and timing of radiotherapy, treatment complications, disease relapse, and relapse-free survival (RFS) were analyzed. Kaplan–Meier lifetable analysis was used to determine survival estimates. There was no significant difference in the 5-year RFS between patients receiving radiotherapy (RT) preoperatively versus postoperatively; 56 ± 15% and 67 ± 12% ($P = 0.12$, Mantel–Cox), respectively. There was no significant difference in the overall survival between patients receiving RT preoperatively versus postoperatively; 75 ± 15% and 79 ± 11% ($P = 0.94$), respectively. Actuarial local control at 5 years for preoperative versus postoperative RT patients was not statistically different; 83 ± 12% versus 91 ± 8% ($P = 0.41$), respectively. Wound complications were more frequent in preoperative RT patients (31%) compared to postoperative RT patients (8%) ($P = 0.0014$, chi-square). Preoperative irradiation was not associated with any benefit in terms of relapse-free survival, overall survival or actuarial local control in this series. A higher incidence of major wound complications was found among patients treated with preoperative irradiation. We recommend that patients with a resectable extremity soft tissue sarcoma be treated with postoperative irradiation, reserving preoperative irradiation for those situations in which either the tumor is initially thought to be unresectable or the original tumor boundaries are obscured.

KEY WORDS: **sarcoma, radiation, surgery, metastasis, local recurrence, complications**

INTRODUCTION

The primary treatment of nonmetastatic, extremity soft tissue sarcomas is surgical resection [1,2]. Rhabdomyosarcoma and Kaposi's sarcoma are not treated the same as classic soft tissue sarcomas and are therefore excluded from this report. In an effort to both improve the local control rates and allow for limb-sparing surgery, adjuvant radiotherapy in combination with conservative surgery is an effective combination of treatment for soft tissue sarcomas. Unlike bone sarcomas, chemotherapy has not been as successful in treating localized soft tissue sarcomas. External beam radiotherapy was initially used; however, more recently brachytherapy [3] intraoperative methods of administration [4–6] and neutron irradiation [7] have been the subject of investigation. External beam

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radiation can be administered either before (preoperative) or after (postoperative) excision of the primary tumor. A number of centers have reported on their experience with postoperative radiation combined with surgery [8–13]. Preoperative radiation has also been combined with conservative surgery and has several theoretical advantages. These include decreased intraoperative seeding of viable cells due to tumor necrosis, a smaller target volume of radiation preoperatively compared to the postoperative wound bed, and tumor mass shrinkage with formation of a dense pseudocapsule facilitating surgical resection [14]. Clinical reviews have established the feasibility of preoperative radiotherapy and suggested that it may be more effective in larger lesions [15,16]. With this in mind, a study was undertaken to report on the experience at the University of Minnesota, in an effort to answer several questions. Is there a difference in either relapse-free survival (RFS) or overall survival for patients treated with preoperative radiotherapy compared to postoperative treatment? Is there a difference in local control for patients associated with either preoperative or postoperative radiation treatment? When patients are grouped according to stage, is there a subset of patients that benefit from radiotherapy given preoperatively? What complications can be associated with preoperative radiotherapy and do they correlate with either a poorer survival or local control?

MATERIALS AND METHODS

Hospital and office records for 112 adult patients aged 18–88 years treated for a nonmetastatic soft tissue sarcoma at the University of Minnesota, 1979–1993, were reviewed. Prior to 1979, radiotherapy was used intermittently and treatment protocols were not uniform; therefore, these patients were excluded. These cases therefore represent those patients who underwent treatment of a primary, nonmetastatic, extremity soft tissue sarcoma at the University of Minnesota and who received adjuvant radiotherapy either preoperatively or postoperatively. Adjuvant chemotherapy was not routinely given to patients for treatment of their primary disease. Table I represents a summary of the two patient groups studied. Their respective diagnoses represent a spectrum similar to most large series of soft tissue sarcomas (Table II). The external beam irradiation techniques and dosage used have been described elsewhere [17]. The average preoperative radiation dose was 4,824 cGy given over an average duration of 38 days. Among the patients who had received preoperative radiotherapy, 25 also were given a postoperative boost averaging 1,660 cGy. The average total radiation dose administered to all 112 patients was 6,281 cGy. All definitive tumor resections were performed by a musculoskeletal oncologic surgeon. The principles of surgical management during this period were defined using anatomic terms of compartmental surgery as described by Enneking et al. [18]. The tumor was approached surgically by the following guidelines, in order of preference: (1) striving to achieve a radical margin when it did not create a significant functional deficit thereby avoiding the need for adjuvant radiation therapy; (2) when this was not possible, striving for a wide surgical margin and supplementing this with radiotherapy; or (3) achieving a marginal anatomic margin as a minimum and supplementing treatment with radiotherapy. The decision as to whether to give radiotherapy preoperatively or postoperatively was made individually after discussion with each patient and a review of all imaging studies. Patients not under active treatment at the University of Minnesota were followed up by review of the medical record at the local or referring physician's office. If this was not possible, direct contact with the patient was established. Follow-up data were successfully obtained on all patients. The average length of follow-up was 5.3 years, with a range of 16 months to 16 years.

All patients were staged according to either Musculoskeletal Tumor Society (MTS) [18,19] or American Joint Committee on Cancer (AJCC) staging criteria [20–22]. Pathological evaluation or radiologic imaging studies were used to ascertain size. Histologic analysis of the resected specimen determined the tumor grade and resection margin.

Complications of treatment were tabulated and categorized according to type of complication, i.e., delayed wound healing, infection, postoperative hematoma, neurapraxia, or fracture. A wound complication was defined as any wound problem which required a secondary operation for treatment, resulted in a delay in radiation treatment of at least one month, or did not heal and persisted for at least six months. For the purposes of analysis, neurapraxias and fractures were not considered to be wound problems.

Statistical analysis was performed using standard software (BMDP) and Kaplan–Meier curves plotted to determine patient survival [23]. All survival estimates are reported using mean and standard deviation with 95 per cent confidence intervals. RFS was defined as the time from diagnosis to either local or distant disease relapse. Overall survival was defined as the time from diagnosis to death from disease. Local recurrence free survival was defined as the time interval from diagnosis to local recurrence. When comparing survival among different patient populations, the Mantel–Cox test was applied [24]. Multivariate Cox regressions were performed to analyze the interaction of several variables upon patient survival. Solo power analysis of the log-rank survival test (BMDP) was used to determine the adequacy of sample size [25].

RESULTS

Relationship Between Timing of Radiotherapy and Survival

Both relapse free survival and overall survival were analyzed. An analysis of the outcome data revealed that the administration of radiotherapy either preoperatively

TABLE I. Soft Tissue Sarcomas: Preoperative Versus Postoperative Radiotherapy: Summary of Study Group Patient Data

	Radiotherapy			
	Preoperative[a]	Postoperative[a]	Preoperative[b]	Postoperative[b]
No. of cases	48	64	28	33
Demographics				
Mean age (years)	47	54	48	51
Sex:				
Male	28	35	20	19
Female	20	29	8	14
AJCC stage				
IA	3 (6.8%)	1 (1.6%)	0	0
IB	4 (8.3%)	7 (11%)	2 (7%)	5 (15%)
IIA, IIIA	13 (27%)	20 (31%)	8 (29%)	9 (27%)
IIB, IIIB	28 (58%)	36 (56%)	18 (64%)	19 (58%)
Resection margin				
Intralesional	9 (19%)	11 (17%)	8 (29%)	3 (9%)
Marginal	10 (21%)	16 (25%)	8 (29%)	16 (48%)
Wide	29 (60%)	37 (58%)	12 (24%)	14 (42%)
Wound complications	15 (31%)	5 (8%)	10 (36%)	2 (6%)
Pearson χ^2	$P = 0.0014$		$P = 0.0037$	

[a] All cases.
[b] Excluding patients who had a prior excisional biopsy.

TABLE II. Soft Tissue Sarcomas: Preoperative Versus Postoperative Radiotherapy: Summary of Patients' Diagnoses (All Cases)

Diagnosis	No. of patients
Malignant fibrous histiocytoma	50
Liposarcoma	24
Synovial sarcoma	13
Neurofibrosarcoma	7
Hemangiopericytoma	4
Leiomyosarcoma	3
Alveolar soft part sarcoma	3
Fibrosarcoma	1
Malignant triton tumor	1
Malignant mesenchymoma	1
Hemangioendothelioma	1
Dermatofibrosarcoma protuberans	1
Epithelioid sarcoma	1
Osteosarcoma, soft tissue	1
Undifferentiated sarcoma	1
Total:	112

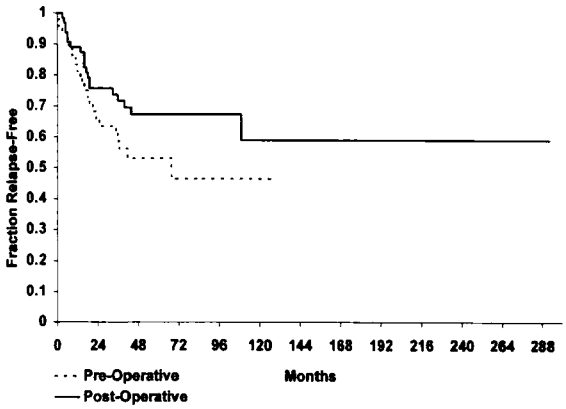

Fig. 1. Relapse-free survival for patients receiving radiotherapy preoperatively versus postoperatively ($P = 0.12$, Mantel–Cox).

or postoperatively was not associated with a difference in RFS (Fig. 1). In addition, a difference in overall survival could not be demonstrated (Fig. 2). At the 5-year time point, RFS for patients receiving preoperative radiotherapy was 56% ± 15% (mean and standard deviation, 95% confidence interval) versus 67% ± 12% for the postoperative radiation group ($P = 0.12$, Mantel–Cox). Likewise, there was no difference in overall survival at 5 years (75% ± 15% versus 79% ± 11%, $P = 0.94$, Mantel–Cox). A trend towards an improved RFS or overall survival in patients receiving preoperative radiotherapy was not present.

Among the 112 patients in this series, 51 presented after an excisional biopsy had been performed at another institution. Since a major portion of the tumor had already been excised, subsequent surgical treatment is frequently compromised and involves a resection of not only the tumor bed but the previous surgical field as well. When these patients were excluded, thereby yielding a more uniform subset of patients (n = 61) who underwent excision of the primary tumor mass at the University of Minnesota, the survival analysis was repeated. No difference in either the RFS or overall survival of this subset of patients could be demonstrated when comparing treatment with preoperative (n = 28) versus postoperative (n = 33) radiotherapy (Figs. 3, 4). At 5 years, the RFS for patients receiving preoperative radiotherapy was

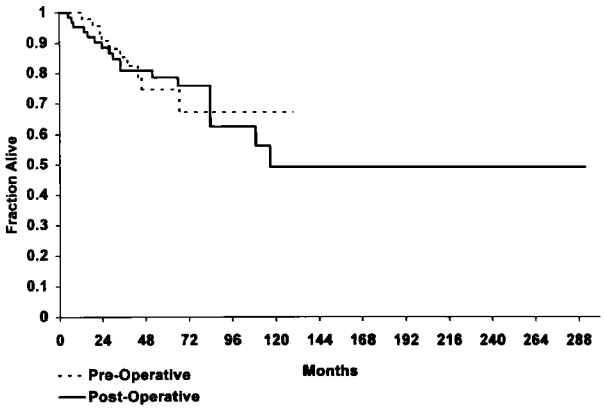

Fig. 2. Overall survival for patients receiving radiotherapy preoperatively versus postoperatively ($P = 0.94$, Mantel–Cox).

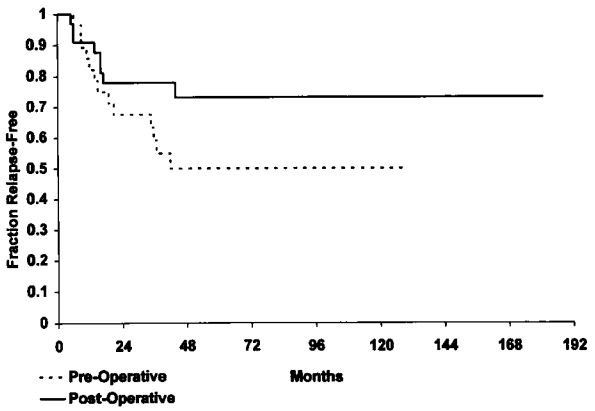

Fig. 3. Relapse-free survival for patients excluding those who underwent excisional biopsy prior to radiation and subsequent residual tumor bed excision ($P = 0.13$, Mantel–Cox).

49% ± 20% and 73% ± 16% for the postoperative treated group ($P = 0.13$, Mantel–Cox). The overall survival at 5 years was 73% ± 21% and 77% ± 17% for the preoperative and postoperative groups, respectively ($P = 0.70$, Mantel–Cox). As one could argue that RFS is the purest form of measuring treatment efficacy, a power analysis was performed on the two groups comparing this parameter. Given the assumptions of a constant patient accrual over a 10-year period, a power of 79–80% is realized for the 2-year RFS data and 44% at the 5-year time point, with a trend suggesting that postoperative radiation is actually associated with a better RFS, rather than preoperative treatment (Fig 3). Therefore, after analyzing the data using both RFS and overall survival, and accounting for the patients who had a previous excisional biopsy, a survival benefit associated with preoperative radiation treatment could not be shown (Figs. 1–4).

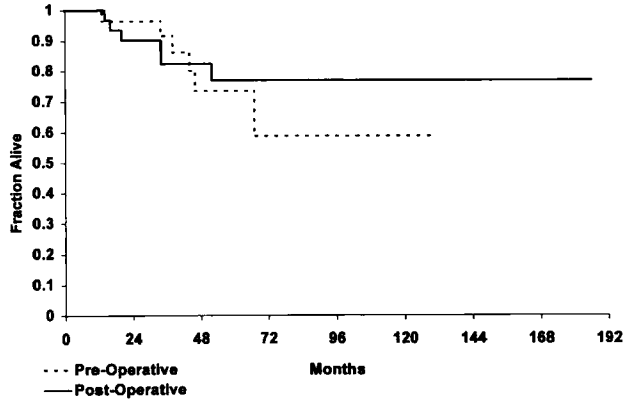

Fig. 4. Overall survival for patients excluding those who underwent excisional biopsy prior to radiation and subsequent residual tumor bed excision ($P = 0.70$, Mantel–Cox).

Relationship Between Timing of Radiotherapy and Survival as Stratified by Tumor Size and Stage

Both the AJCC and MTS staging systems are commonly used for soft tissue sarcomas. The principal difference is the use of tumor size, and not anatomic compartment, in the AJCC system as well as a four-tiered grading system compared to three for the MTS system. Prior studies have suggested that the benefits of preoperative radiation may be maximal for the patients with large tumors [1,15]. When the patient cohort was grouped according to AJCC staging criteria, taking into account tumor size, there was a strong relationship between advancing stage and shorter survival as defined by both RFS and overall survival, regardless of the timing of radiotherapy. The 5 year RFS for stage IIA–IIIA tumors treated with preoperative radiotherapy was 66% ± 28% versus 84% ± 16% for the postoperatively treated group ($P = 0.23$, Mantel–Cox) (Fig. 5). The 5 year RFS for stage IIB–IIIB tumors treated with preoperative radiotherapy was 42% ± 20% versus 54% ± 18% for the postoperatively treated group ($P = 0.33$, Mantel–Cox) (Fig. 5). Similar results were noted when overall survival instead of RFS was evaluated (Fig. 6). Therefore, when the relationship between pre- or postoperative radiotherapy and survival was studied for patients in each respective AJCC stage, there was no difference statistically in either RFS (Fig. 5) or overall survival (Fig. 6).

Relationship Between Timing of Radiotherapy and Local Recurrence

The number of local recurrences in the preoperative radiation group was 7 (15%) and in the postoperative group, 6 (9%). As noted above, an excisional biopsy prior to definitive resection may complicate treatment, six local recurrences were in this group of patients (Table III). Actuarial analysis of the local recurrence-free survival of patients did not reveal any statistical difference between

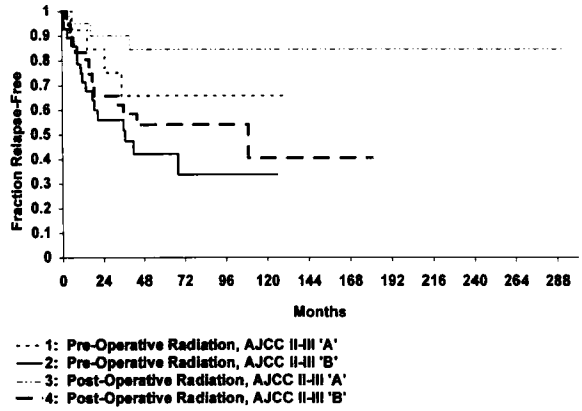

Fig. 5. Relapse-free survival of patients stratified by AJCC stage and timing of radiotherapy; AJCC IIA + IIIA patients, preoperative versus postoperative radiotherapy ($P = 0.23$, Mantel–Cox); AJCC IIB + IIIB patients, preoperative versus postoperative radiotherapy ($P = 0.33$, Mantel–Cox).

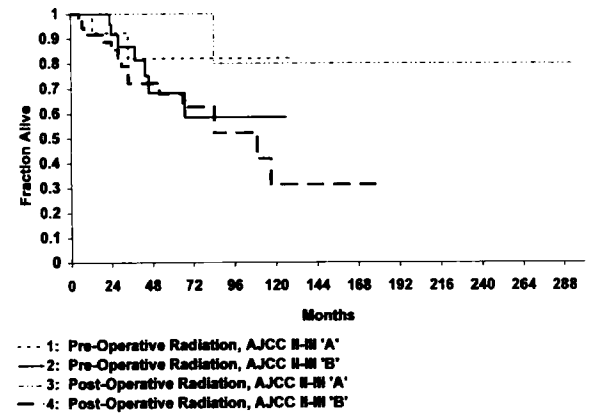

Fig. 6. Overall survival of patients stratified by AJCC stage and timing of radiotherapy; AJCC IIA + IIIA patients, preoperative versus postoperative radiotherapy ($P = 0.29$, Mantel–Cox); AJCC IIB + IIIB patients, preoperative versus postoperative radiotherapy ($P = 0.60$, Mantel–Cox).

TABLE III. Soft Tissue Sarcomas: Incidence of Local Recurrences Among All Patients According to Timing of Radiation and Previous Excisional Biopsy

	No prior excisional biopsy	Prior excisional biopsy
Preoperative radiation	5	2
Postoperative radiation	2	4

the preoperative and postoperative radiation groups (Fig. 7). The proportion of patients free of local recurrence at five years for the preoperative radiation group was 83% ± 12% versus 91% ± 8% for the postoperative radiotherapy patients ($P = 0.41$, Mantel–Cox). No trend favoring either treatment arm was found.

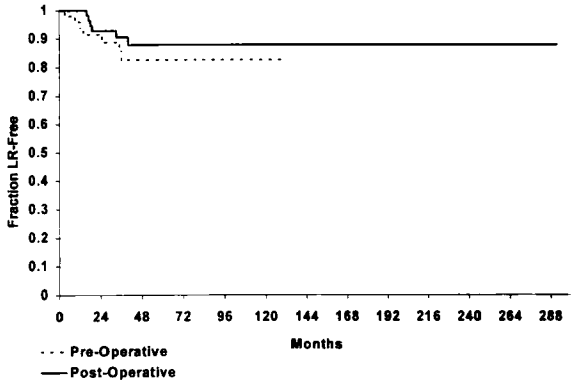

Fig. 7. Local recurrence-free survival of patients receiving radiotherapy preoperatively versus postoperatively ($P = 0.41$, Mantel–Cox).

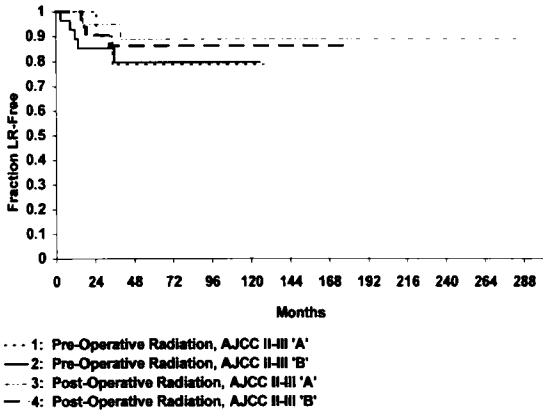

Fig. 8. Local recurrence-free survival of patients stratified by AJCC stage and timing of radiotherapy; AJCC IIA + IIIA patients, preoperative versus postoperative radiotherapy ($P = 0.48$, Mantel–Cox); AJCC IIB + IIIB patients, preoperative versus postoperative radiotherapy ($P = 0.46$, Mantel–Cox).

Relationship Between Timing of Radiotherapy and Local Recurrence as Stratified by Tumor Stage

The issue of local recurrence is of more importance for larger tumors. Therefore, the same analysis was repeated when the patients were stratified according to AJCC stage. Figure 8 reveals that when the proportion of patients free of local recurrence is grouped according to AJCC stage, no difference in local control could be established comparing preoperative and postoperative radiation treatments.

Five-year local recurrence-free survival for AJCC stage IIA and IIIA tumors treated with preoperative radiation was 79% ± 26% and for postoperative radiation was 89% ± 15% ($P = 0.48$, Mantel–Cox). For larger tumors, i.e. AJCC stage IIB and IIIB tumors, the 5-year local recurrence free survival was 80% ± 16% in the preoperative group and 86% ± 13% in the postoperative group ($P = 0.46$, Mantel–Cox) (Fig. 8).

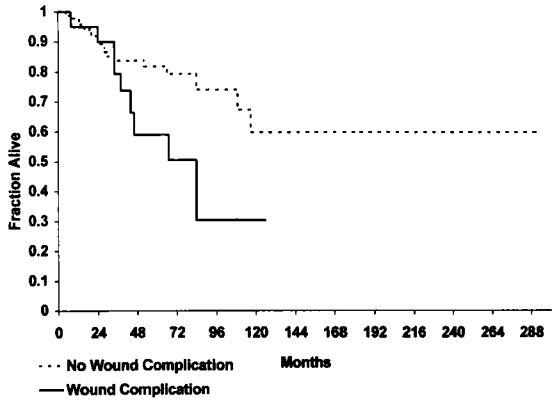

Fig. 9. Overall survival for patients with and without a wound complication ($P = 0.023$, Mantel–Cox).

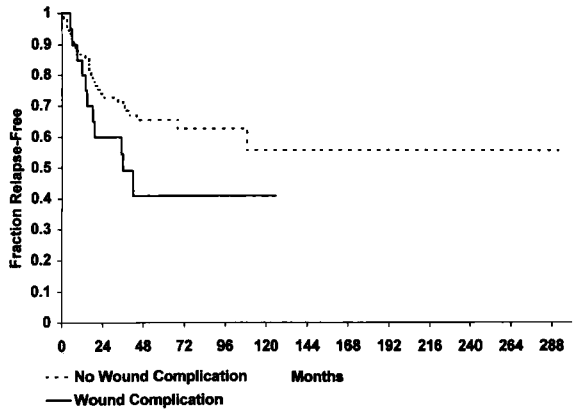

Fig. 10. Relapse-free survival for patients with and without a wound complication ($P = 0.095$, Mantel–Cox).

Complications and Survival

Wound complications occurred in 20 patients, 15 in the preoperative radiotherapy group and 5 in the postoperative group. This difference was highly statistically significant ($P = 0.0014$, pearson χ^2). The presence of a wound complication was associated with a statistically significant decrease in overall survival (Fig. 9) ($P = 0.02$, Mantel–Cox), while only a trend toward a poorer RFS was demonstrated Fig. 10, ($P = 0.095$, Mantel–Cox).

In order to isolate the impact of a wound complication, patients were stratified according to the timing of their radiation treatment. When evaluating wound complications among only patients receiving preoperative radiation, a difference in RFS or overall survival was not evident (Figs. 11 and 12). Among patients receiving postoperative radiation, however, the findings were different. A trend between a wound complication and a poorer RFS was noted although this did not reach statistical significance ($P = 0.08$, Mantel–Cox) (Figure 11). When looking at overall survival, though, this trend correlating

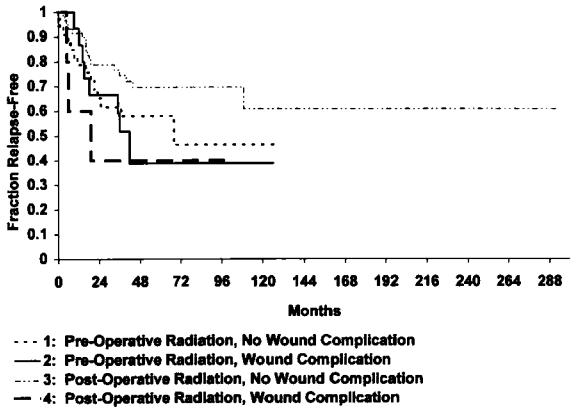

Fig. 11. Relapse-free survival of patients stratified by presence of a wound complication and timing of radiotherapy; preoperative radiotherapy patients, no wound complication versus wound complication ($P = 0.69$, Mantel–Cox); postoperative radiotherapy patients, no wound complication versus wound complication ($P = 0.08$, Mantel–Cox).

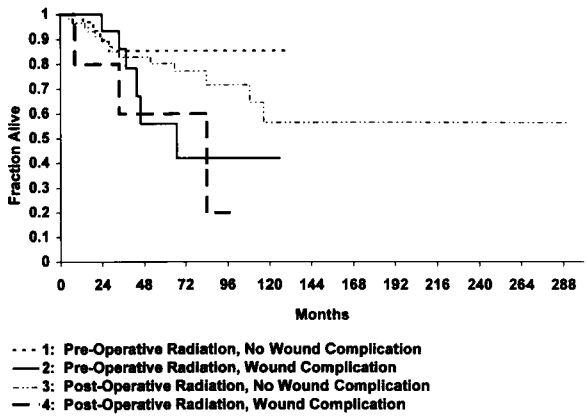

Fig. 12. Overall survival of patients stratified by presence of a wound complication and timing of radiotherapy; preoperative radiotherapy patients, no wound complication versus wound complication ($P = 0.12$, Mantel–Cox); postoperative radiotherapy, no wound complication versus wound complication ($P = 0.03$, Mantel–Cox).

a wound complication with a poorer survival was statistically significant ($P = 0.03$, Mantel–Cox, Figure 12). This would imply that while wound complications are more frequent in the patients getting preoperative radiation, the presence of a wound complication after surgical excision of the tumor is more devastating in those patients who have not yet received any radiation. In an attempt to analyze this finding, a multivariate Cox regression, including the covariant AJCC stage, timing of radiation, and wound complication was performed. For overall survival, both AJCC stage and the presence of a wound complication were independent prognostic factors.

DISCUSSION

Adjuvant radiotherapy combined with surgical resection is a standard treatment method for the management

of soft tissue sarcomas [26,27]. Overall RFS rates of 70–80% have been reported at several centers [15,28]. Lindberg et al. [29] developed the use of adjuvant postoperative radiation therapy in the 1960s. More recently, preoperative treatment with radiation alone or in combination with chemotherapy has been investigated [15,30–32]. Although preoperative radiation has several theoretical advantages, phase III randomized trials demonstrating an improvement in survival are lacking and therefore this treatment rationale remains controversial. In the past, patients at the University of Minnesota were treated with postoperative radiation in conjunction with conservative surgery. Starting in 1980, preoperative radiation was utilized, initially, for patients with larger tumors where a radical margin was not feasible and then gradually used for other size lesions. This report is a review of the experience with both preoperative and postoperative radiation therapy. An acknowledged deficiency is the preselection bias inherent in all review studies, which makes it difficult to draw any definite conclusions. An examination of the two treatment arms, however, does reveal relatively well balanced study groups with equal proportions of patients in each group when classified by stage and surgical margin (Table I).

Preoperative radiotherapy was not associated with any improvement over postoperative radiation in either RFS, overall survival, or local control in this series. The lack of a statistical difference in survival could be attributable to several possibilities. Either preoperative therapy does not offer any therapeutic benefit or this study failed to show an advantage due to inadequate sample size, preselection bias, or an unusual patient population. While this series is smaller than other reported series, a major effort was made to study only a restricted, well-defined cohort of cases treated in a uniform manner. When a power analysis was performed comparing the RFS of this restricted group of patients (Fig. 3), the sample size appeared to be adequate to demonstrate a difference between the two treatment groups if one was present. Given the fact that a trend was demonstrated actually favoring the RFS of patients receiving postoperative and not preoperative radiation, it is unlikely that preoperative radiation offers any survival benefit over the postoperative treatment. Preselection bias cannot be completely eliminated from any nonrandomized study, however, there is justification for performing this study. Although slightly more patients received postoperative radiation when compared to the patients receiving preoperative radiation, the two study groups are proportionately similar with regard to known prognostic factors (Table I).

In an effort to identify a uniform group of patients who might benefit from preoperative radiation, patients were stratified by stage and compared among their respective stages. The AJCC staging system was used as tumor size is a major defining factor in this system and it has been suggested that preoperative radiation would be more appropriate in larger lesions [33]. Analysis of this patient cohort did not reveal any subgroup of patients in which preoperative radiation correlated with an improvement in either RFS or overall survival or local control, regardless of tumor stage. It can be inferred that since tumor grade, size, and confinement to a single anatomic compartment are the principle determinants of stage, none of these variables would be successful in defining a subset of cases for which preoperative radiation would be optimal. There is little likelihood that preoperative radiation is associated with a major improvement in survival. In support of this conclusion is the finding that a difference in survival was not present, even after the patients were grouped according to the most likely prognostic factors to affect treatment.

When patients who had an excisional biopsy were excluded, yielding a more well-defined group of patients, the analysis yielded the same conclusion. In addition, a trend, was actually noted correlating *postoperative*, and not *preoperative*, radiotherapy with an improved relapse free survival, indicating that the likelihood of the reverse being true is remote.

Preoperative radiation treatment may be useful for patients who present with lesions not amenable to a limb-salvage procedure due to the proximity of vital neurovascular structures. It was not possible in this review to determine objectively whether preoperative radiation salvaged any such cases. The histologic response of tumors to preoperative radiation has been shown to be dependent on both size and tumor grade with larger, higher-grade lesions responding more favorably [34]. The radiographic response of tumors to preoperative radiation has been evaluated at the University of Minnesota with a reduction in tumor volume noted in 40%, no change in volume in 45%, and an increase in volume in 15% of cases [35]. This is relatively similar to the University of Florida results, which found tumor regression in 60%, no change in size in 28%, and tumor enlargement in 12% of cases [31]. As lesions that are initially unresectable usually are both large and high grade, this may represent a situation in which preoperative radiation has a significant benefit.

Several other centers have compared preoperative versus postoperative radiation for soft tissue sarcomas. Suit et al. [15] reported the Massachusetts General Hospital (MGH) results and stated that while preoperative or postoperative radiation did not correlate with any difference in survival, the local control of patients with larger tumors was improved with the use of preoperative radiation. The 5-year local control result for patients with AJCC stage IIA/IIIA tumors was 100% and 98%, respectively, for the preoperative and postoperative groups. Patients with AJCC stage IIB/IIIB and IVA tumors had 5-year local control figures of 93% and 68%, respectively, for the preoperative and postoperative groups. While these re-

sults may appear different from the University of Minnesota series, it is difficult to make a direct comparison for several reasons. Both studies are retrospective and therefore subject to the same deficiencies. In addition, as Kaplan-Meier survival plots and Mantel-Cox statistical analyses were not presented in the MGH series, the statistical significance of any differences in local control rates is unknown. The inclusion of stage IVA patients in the MGH study group is probably not significant, as the number of patients in this category was small. Another possibility for different results between the two series may be technical variations in either surgery or administration of radiation. As strict oncologic principles were adhered to by surgeons at both institutions, there are probably no significant differences in technique. The methods and dosage used for external beam irradiation at the University of Minnesota [17] also are similar to those described by Suit et al. [36]. The Mayo Clinic reported their results with both preoperative radiation and postoperative radiation for one hundred eighty-nine patients treated during 1981–1991 [37]. Their patient cohort was similar to ours in terms of AJCC stage, radiation dose, and study period, although the preoperative and postoperative radiation groups were not well balanced, with a greater proportion of larger tumors being treated preoperatively. An actuarial overall survival of 65% and local control of 86% at 5 years was noted and local control was not influenced by whether or not radiation was administered preoperatively or postoperatively. These findings are similar to our results. Radiation therapy may be of greatest importance in regards to local tumor control. In our series, when preoperative radiation was compared to postoperative radiation to see whether or not any improvement in local control was present, no therapeutic benefit could be demonstrated (Fig. 7). When stratified according to stage and tumor size, again no benefit was found to be associated with preoperative over postoperative radiation.

Several other centers have reported their experience using preoperative radiation, and our results compare favorably. The University of Florida studied their results using preoperative radiation in a cohort of 58 patients, which is similar to ours with respect to diagnosis, grade, and stage [31]. Overall survival at 5 years was 39% for patients with AJCC stage IIA tumors and 46% for AJCC stage IIB tumors. Although direct comparisons are difficult, both our results and those of the MGH would appear to be better. Actuarial local control is somewhat difficult to compare between the Florida and Minnesota series due to reporting differences. The local recurrence-free interval for University of Florida cases with a negative or positive margin was 92% and 66%, respectively, at 5 years. For all patients treated with preoperative radiation at the University of Minnesota, the five year local recurrence free interval was 83%. The M.D. Anderson Hospital initially began using preoperative radiation for tumors not readily resectable and expanded their indications during 1970–1984 [32]. In 110 patients, overall survival at 5 years for patients with tumors less than five centimeters size, between five to fifteen centimeters, and greater than five centimeters was 90%, 65%, and 48%, respectively, as extrapolated from their survival curve. Actuarial data for local recurrence was not reported but the incidence was 10% overall. Therefore, comparison of the preoperatively treated patients in our series does not differ markedly from other reported centers.

The disadvantage of using preoperative radiation is a higher incidence of wound complications. Wound hematomas, seromas, infection and breakdown are all in part due to the altered wound healing potential of irradiated tissue. In this series, there was a correlation between a wound complication and a decreased overall survival. Cox multivariate regression demonstrated that this was an independently significant variable for overall survival, but not for RFS. The higher incidence of wound complications in patients receiving preoperative radiation is in agreement with the reports from the Massachusetts General Hospital and M.D. Anderson Hospital [15,32]. The negative impact of a wound complication cannot be underestimated. A wound complication results in a delay of radiation or chemotherapy, a delay in physiotherapy to restore motion and function and prolonged hospitalization, and can be psychologically devastating. With improvement in surgical technique and more aggressive use of local and free muscle flaps, wound problems may become more manageable. Nonetheless, the additional financial costs associated with either muscle flaps or treatment of a wound complication are economically unappealing.

In this study, preoperative radiation therapy was not associated with a definite therapeutic benefit in terms of improved RFS or overall survival when compared with postoperative radiation therapy. In addition, the incidence of local tumor control was statistically the same regardless of when the radiation was administered. Although the potential advantage of preoperative radiotherapy has not been conclusively shown in clinical trials, it may prove to be most beneficial in patients with tumors not initially amenable to a limb-salvage procedure as any tumor shrinkage may enable subsequent tumor excision. Another scenario in which preoperative radiation may be most beneficial is in the patient who has had an excisional biopsy where the tumor has been "shelled out," resulting in an intralesional margin. Other centers have indicated that while preoperative radiation is not associated with any survival benefit, its main advantage is in local control of the tumor [15,38]. These findings are consistent with a number of studies which have questioned the relationship between a local failure and survival for soft tissue sarcomas [39–44]. Our study fails to show any local control

benefit for preoperative radiation. Even if a small benefit does exist, it is questionable whether the increased risk of a wound complication justifies this small incremental local control benefit. The impact of a wound complication is magnified if it delays the administration of a systemic treatment such as chemotherapy. As more effective systemic treatments are developed for soft tissue sarcomas, this will become a crucial issue. As exemplified by this series, the higher incidence of wound complications in patients treated with preoperative radiotherapy remains a significant concern. For most soft tissue sarcoma patients who present with tumors not intimately associated with a vital structure, we believe that administration of radiation postoperatively is justified as a clear survival benefit for preoperative radiation has not yet been demonstrated and a higher risk of wound complications is realized.

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